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ASSESSMENT OF THE PHARMACODYNAMICS OF INTRANASAL, INTRAVENOUS
AND ORAL SCOPOLAMINE

Final Report

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ABSTRACT

Space motion sickness is an important issue in the space medical sciences program. Although scopolamine has been documented to be an effective antimotion sickness agent, limited information is available regarding the pharmacodynamics of scopolamine and the relationship between the pharmacodynamics and the pharmacokinetics of the drug. One of the objectives of the ongoing clinical experimental protocol "Pharmacokinetics of Intranasal Scopolamine in Normal Subjects" is to evaluate the pharmacodynamics of scopolamine using salivary flow rate and pH profiles and cognitive performance tests as pharmacodynamic parameters.

Normal volunteers collected saliva and performed the NTI Multiresource Performance Battery test at designated time intervals to establish control salivary flow rates, salivary pH profiles, and the characteristics of the learning curve for the performance program under normal conditions. Salivary flow ranged between 50 to 60 ml/hr with pH ranging between 6.5 to 7 over a 2 hour period. Preliminary assessment of the performance data from the first few volunteers suggests that the duration of the learning curve is short reaching a plateau after two test sessions for task one and five to eight test sessions for task two.

In the clinical part of the study, saliva samples and performance test scores are collected from healthy nonsmoking subjects after receiving a single 0.4 mg dose of either intranasal, intravenous, or oral scopolamine. Both salivary flow rate and pH decreased as a function of time after administration of all the three dosage forms. The pharmacodynamic effect as indicated by salivary flow rate and pH was the greatest after intravenous administration and the least after oral administration. Preliminary analysis of the performance parameters for a limited number of subjects indicates that there is no significant change in task one or task two scores following the administration of any of the three dosage forms. However, the mean correct response times for tasks following the transition from one task to another appear to be slightly longer during the first few hours following scopolamine administration.

Preliminary evaluation of this limited data suggests that salivary flow rate and pH are good pharmacodynamic indicators for scopolamine, and that intranasal scopolamine produces a reliable and consistent pharmacodynamic effect. Limited performance data collected so far suggest that scopolamine does not decrease cognitive function as measured with the NTI Multiresource Performance Battery. Results from the study may be useful in identifying and selecting effective dosage forms for the management of SMS.

INTRODUCTION

Space motion sickness (SMS) is a major concern in the space medical sciences program. Approximately 50-60% of astronauts experience SMS, which usually affects astronauts during the first three days of flight and may be severe enough to compromise the operational performance of the astronaut (1). Use of antimotion sickness drugs in flight has been limited by drug ineffectiveness or by undesirable side effects that impair the operational performance of the astronaut. Scopolamine, an anticholinergic drug, has been documented to be an effective antimotion sickness agent (2,3). It has been suggested that scopolamine interrupts the acetylcholine-dependent neurotransmission of information from the vestibular organs to the vomiting centers of the brainstem (4,5). At present, scopolamine (0.4 mg) in combination with dextroamphetamine (5 mg) is administered orally as a capsule for the prophylaxis and treatment of SMS. An important side effect of operational significance induced by scopolamine is the impairment of cognitive performance. Another side effect that is not of clinical importance but can be used as a pharmacodynamic indicator is inhibition of salivary secretion.

Although a veteran drug, the pharmacodynamics of scopolamine and the relationship between the pharmacokinetics and the pharmacodynamics of the drug have not been well characterized. Several investigators have documented that oral scopolamine impairs cognitive performance; the techniques used are complex and time-consuming (6-12). Identification of a sensitive and convenient method for the assessment of drug-induced performance changes would be helpful in establishing the selection criteria for drugs used for the prophylaxis and treatment of SMS and also for the pharmacodynamic assessment of these drugs during space flight. The project therefore was designed to 1) establish salivary parameters in control subjects using the Sarstedt Salivette system, 2) to determine cognitive performance in control subjects using the NTI Multiresource Performance Battery, and 3) to compare the effect of a 0.4 mg dose of intranasal, intravenous, and oral scopolamine on these parameters.

MATERIALS AND METHODS

Scopolamine Study

A conventional clinical IND protocol was designed to evaluate the pharmacokinetics and bioavailability of the three dosage forms. Healthy nonsmoking male subjects ranging between 18 to 40 years of age are participating in the study. All subjects passed an Air Force Class III physical examination, including hematology, electrocardiogram, urinalysis, and biochemistry tests before admission to the study. The study protocol was approved by the human research review committees of NASA-JSC and the St. John Hospital. Informed consent was obtained from all the subjects prior to the study.

The study consists of an intranasal, an intravenous, and an oral treatment phase. A 0.4 mg dose is used in all three treatment phases. Each 24 hour treatment phase is separated by at least a two week period. The treatments are administered in a predetermined randomized crossover design. Oral scopolamine was customed manufactured by AC Engle & Co, Houston, Texas, intravenous scopolamine dosage form was procured from a pharmacy, and intranasal scopolamine was customed-manufactured by the Pharmaceutics Department of the University of Houston, Houston, Texas. Subjects are admitted to the hospital the night before each study period. Each subject is given written and oral instructions for the Multiresource Performance Battery computer program and trained until they are comfortable with the computer keyboard and the program. Mixed saliva is collected over a two minute interval using the Sarstedt Salivette system (a cotton swab collection system) before and at 5, 10, 15, 20, 30, 45, 60, 90 minutes and 2, 3, 4, 5, 6, 8, 10, and 12 hours after dosing. The Multiresource Performance Battery test is taken pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours post-dose.

The investigational Multiresource Performance Battery computer program was obtained from NTI, Inc. The program runs on a portable personal computer and is designed to test the higher cognitive functions most likely to be affected by centrally active drugs. The program consists of two timed tasks presented pseudosimultaneously with an attention allocation indicator. Both tasks appear on the screen simultaneously with two bars of differing height at the bottom center of the screen. The active task is identified as the task on the side of the screen with the highest bar. The math task appears on the left of the screen and consists of a two step (addition, subtraction, or combination) single digit math problem. The key "z" is pressed if the answer is less than five and the key "v" is pressed if the answer is greater than five. The memory task appears on the right of the screen and consists of two single digit numbers separated by a line. The task is to determine if the numerator of the current active task matches the denominator of the prior active task. The key "m" is pressed if the numbers match and the key "/" is pressed if the numbers do not match. The test battery consists of 100 randomly generated tasks with an approximately equal distribution between the two tasks. Each 100 task test battery is preceded by a randomly generated 20 task warm-up battery that may be repeated until the subject no longer feels his performance is improving. The program allows for a maximum of five seconds for a response before randomly changing to a new test in the same task or to the alternate task. Performance parameters include the percent correct, incorrect and timed out and the mean correct response times for both tasks as well as the percent correct, incorrect, and timed out and the mean correct response times for the transitions to each task and for the total transitions.

Control Data Collection

Because the NTI Multiresource Performance Battery is a new investigational program, no data exists on the learning curve with the program. Preliminary analysis of data from the first few subjects suggested a learning curve interval which may mask the drug effect. Another contributing factor of variability may be the time of day (i.e. morning vs. afternoon). To address these issues, ten normal volunteers were selected for twice daily testing for ten days. Each subject received verbal and written instructions for the Multiresource Performance Battery and was then tested twice daily (in the morning and afternoon) for a total of 20 tests over a three week period. The performance parameters (percent correct, incorrect and timed out; mean correct response times; and transition percents and response times) for each task will be analyzed and the learning curve will be characterized.

To evaluate whether the repeated collection of saliva with the Salivette system during the first hour of the study would alter salivary flow dynamics, four volunteers repeated the saliva sampling protocol for the clinical study. Salivary volume and pH were measured and flow rate calculated for each time period.

PRELIMINARY RESULTS

Control Data

Salivary Data. Sample collection and data analysis for the salivary data was completed. Salivary flow rate and pH appears to be relatively constant over the twelve hour sampling period using the Salivette system (Figure 1). Mean flow rate ranged between 50 to 60 ml/hr and mean salivary pH ranged between 6.5 and 7.0. No significant changes in flow rate or pH were noticed as a function of either the frequency of samples or time of day.

Performance Data. Data collection for this parameter is still in progress. Preliminary assessment of the data from the first few trials suggests that there is a subject dependent learning pattern with the program. In some individuals there was no improvement which suggests that these subjects did not exhibit a learning curve, but in others there was an apparent learning curve. There was a considerable intersubject variability in scores, but plateau scores were relatively constant for each individual. The learning curve appears to plateau after two test sessions with the math task and after five to eight test sessions with the memory task. There does not appear to be any difference between scores achieved in the morning versus scores achieved in the afternoon.

Scopolamine Study

Salivary Data. A limited number of subjects (intranasal n=8; intravenous n=7; oral n=8) have completed the study so far.

Preliminary results from these subjects were evaluated and reported here. Although all three dosage forms of scopolamine appear to decrease salivary flow rate and salivary pH, differences are apparent between the dosage forms (Figure 2). Intravenous scopolamine markedly inhibited salivary flow rate and lowered salivary pH. Flow was nearly totally inhibited in the first 15 minutes following administration of the drug, with a slow recovery to pre-dose flow in four to six hours. Salivary pH fell from the pre-dose mean of 6.6 to 5 in the first 90 minutes following intravenous administration of the drug, with slow recovery to pre-dose value by five hours. Intranasal scopolamine lowered salivary flow to about 5 ml/hr in about one hour with a slow recovery at nearly the same rate as with intravenous scopolamine. Salivary pH fell from the pre-dose mean of 6.7 to 4.8 in the first 90 minutes following the intranasal administration of the drug, which was a slightly larger decline than with the intravenous dosage form. Oral scopolamine caused a small decrease in flow in about one hour, with recovery to pre-dose flow by two hours. Salivary pH fell slightly from the pre-dose mean of 6.7 to 6.3 in the first three hours following oral administration.

Performance Data. Preliminary analysis of the performance parameters for the first few trials suggests that there is no change in task one or task two scores (percent correct, percent incorrect, percent timed out) following the administration of intranasal, intravenous, or oral scopolamine. None of the three dosage formulations adversely affected the mean correct response times for task one or task two. However, the mean correct response times for performance of task one following transition from task two and for performance of task two following transition from task one appear to be slightly longer in the first few hours following drug administration (Figure 3).

DISCUSSION

The flow rate of mixed saliva following the administration of anticholinergic drugs has been reported but was not well characterized. Grundhofer and Gibaldi found that oral administration of the anticholinergic drugs propantheline and hexocyclium lowered salivary flow rate by approximately 75% in two hours, with a gradual recovery to pre-dose rate by four to six hours (13,14). Brand *et al* reported that the administration of scopolamine at oral doses of 0.42 and 0.7 mg lowered salivary flow rate to approximately 50% of baseline by two to three hours (15). Gordon *et al* found that transdermal scopolamine lowered salivary flow rate by about 50% after 12 to 18 hours of transdermal administration (16). The present investigation is the first of its kind to utilize salivary characteristics for pharmacodynamic evaluation of dosage forms of scopolamine. Limited data collected so far indicate that there are differences in the pharmacodynamic effect as suggested by salivary flow rate after intranasal, intravenous, and oral administration of scopolamine, with a fast and pronounced effect from the

intravenous dosage form and a relatively slow and minimal effect from the oral dosage form. This appears to reflect the differences in pharmacokinetics and bioavailability of the three dosage forms.

Salivary pH depends on salivary flow (17). Therefore, it is anticipated that salivary pH decreased with the decreased flow rate. However, the lowest mean salivary pH following the intravenous and intranasal administration of scopolamine is lower than the 5.8 reported by Kreusser for unstimulated salivary glands. Salivary pH appears to be a good indicator of the differences in pharmacodynamic effect of different dosage forms, which may be a function of the pharmacokinetic properties of the three dosage forms.

Although psychometric testing has been used to assess the pharmacodynamic effects and side effects of centrally active drugs, limited information is available regarding the shapes and duration of learning curves or their interference in repeated measures testing. Schulz suggested that subjects should be given a period of familiarization with the testing procedures followed by repeated testing until the subjects achieve a predetermined coefficient of variation (18). Our results suggest that there is a learning curve with both tasks in our study, and that although there is some intersubject variability in individual plateaus for efficiency, the subjects require several tests to reach peak efficiency with the memory task. This data suggests that subjects require more experience with the program than is currently being provided prior to testing after administration of the drug.

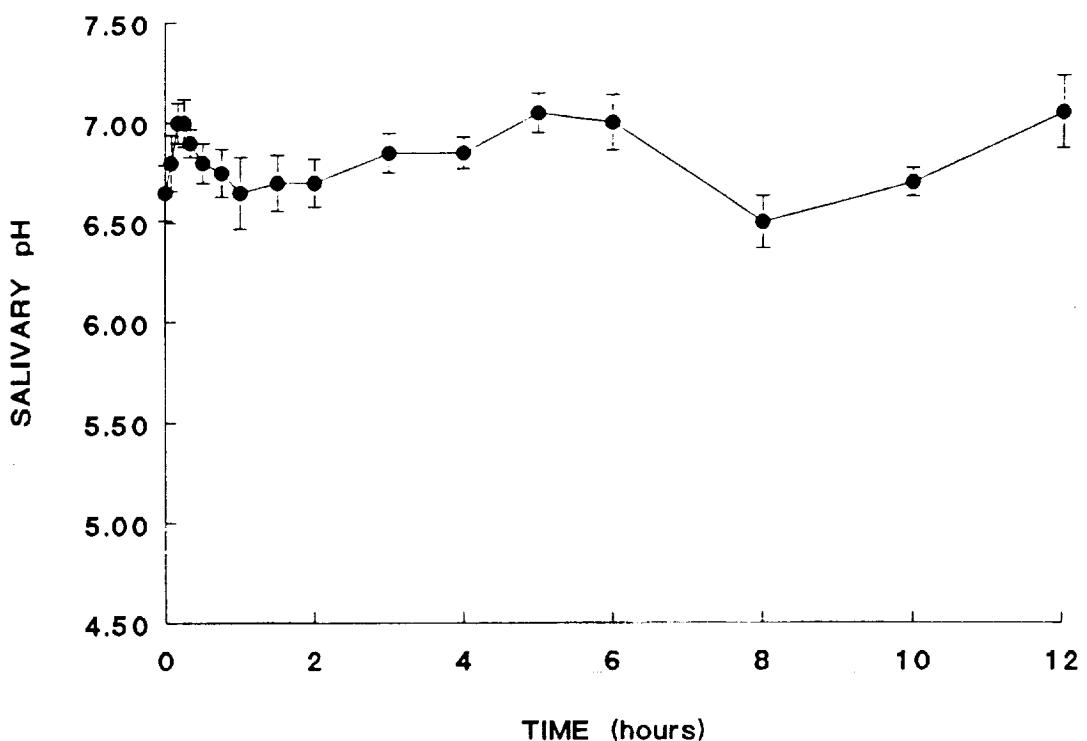
Traditional psychometric testing has documented that oral scopolamine impairs cognitive performance (6-12). Acetylcholine appears to be important for the processes of sustained attention and vigilance (7,19,20) as well as stimulus processing and memory storage (21-26). Although early studies indicated that scopolamine impaired longterm recall (23,27), more recent studies indicate that scopolamine impairs tasks involving sustained continuous attention or the storage of new information into memory rather than recall of information memorized before drug administration (8,11,12). In an investigation using a different investigational NTI performance battery, it was reported that scopolamine did not affect performance when using reaction time as a parameter for either spatial or verbal resources, but that scopolamine did impair the attention allocation system (28). Although preliminary, present data appear to support the findings that scopolamine impairs tasks requiring sustained continuous attention and processing of newly memorized information.

CONCLUSION

Limited information regarding the pharmacodynamics of scopolamine has been reported. This study was designed to quantitate the differences in pharmacodynamics between the intranasal,

intravenous, and oral dosage formulations of scopolamine. Data analysis for the completed studies will be performed and the relationship between the pharmacodynamics and the pharmacokinetics of the drug will be determined. It is anticipated that the results from these studies will provide new information that will be useful in the selection of appropriate drugs and dosage forms for the management of space motion sickness.

BASELINE SALIVARY pH



BASELINE SALIVARY FLOW

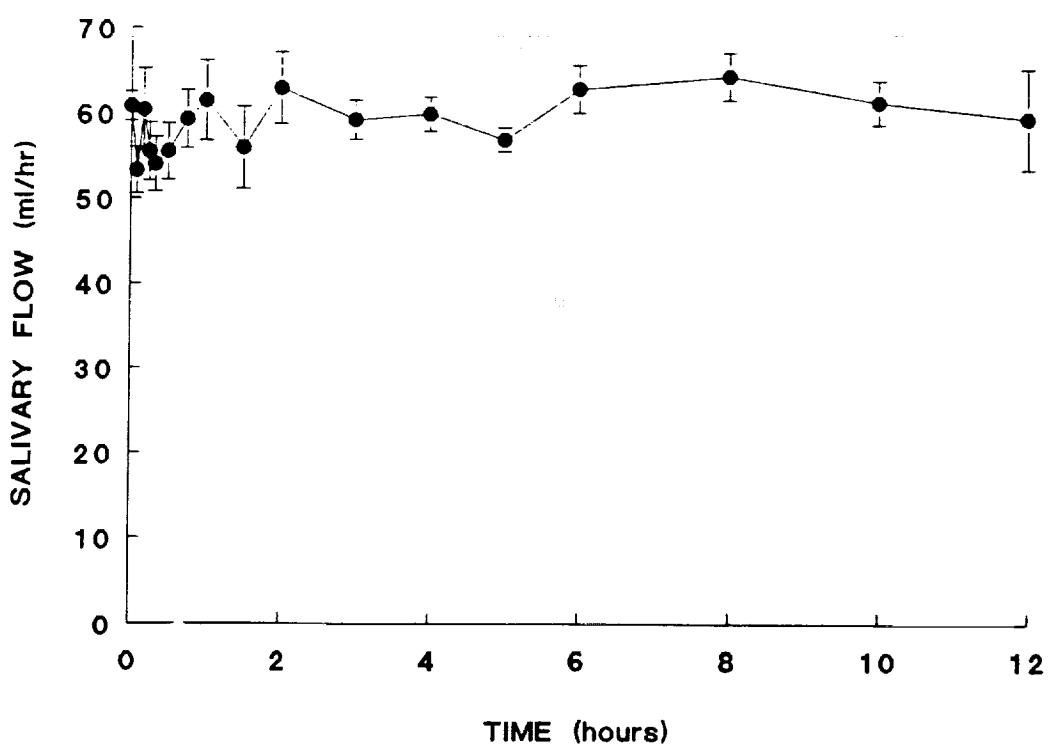
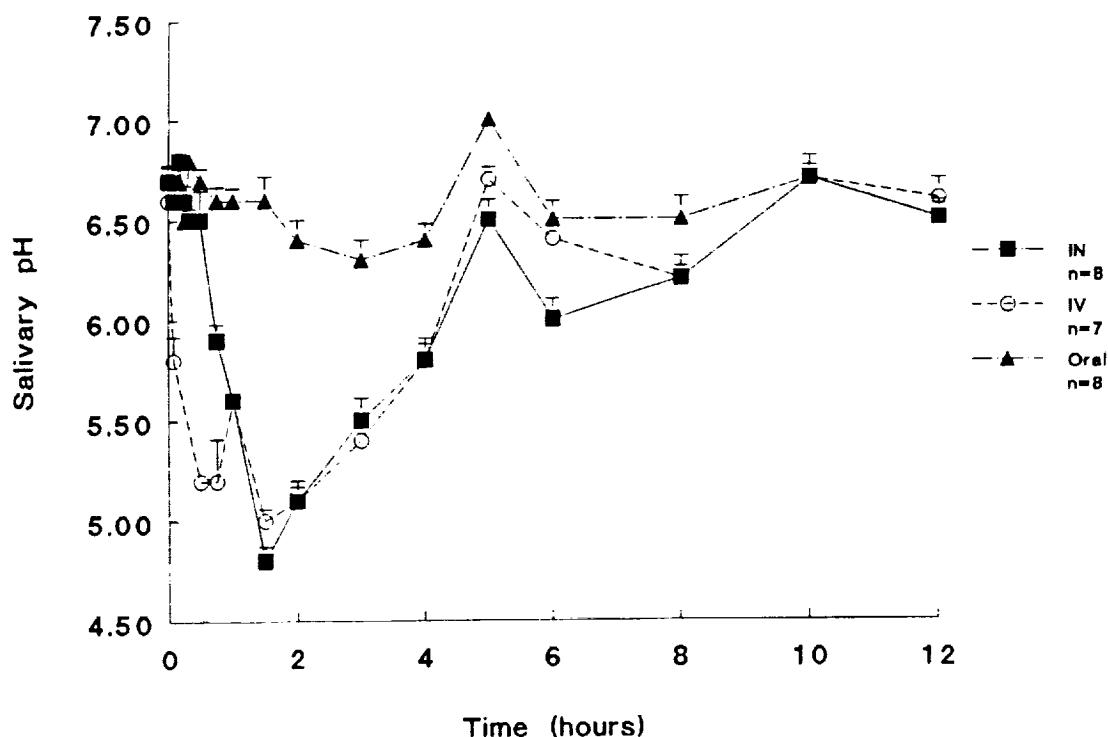


FIGURE 1.-BASELINE SALIVARY FLOW RATE AND pH.

Salivary pH



Salivary Flow

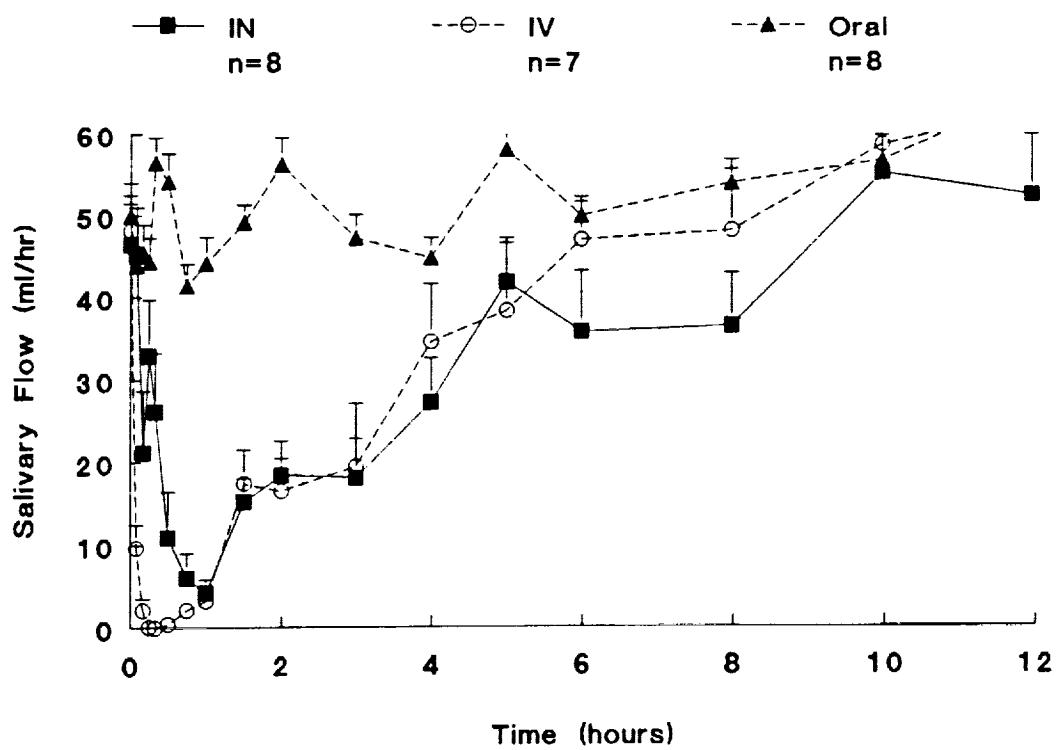
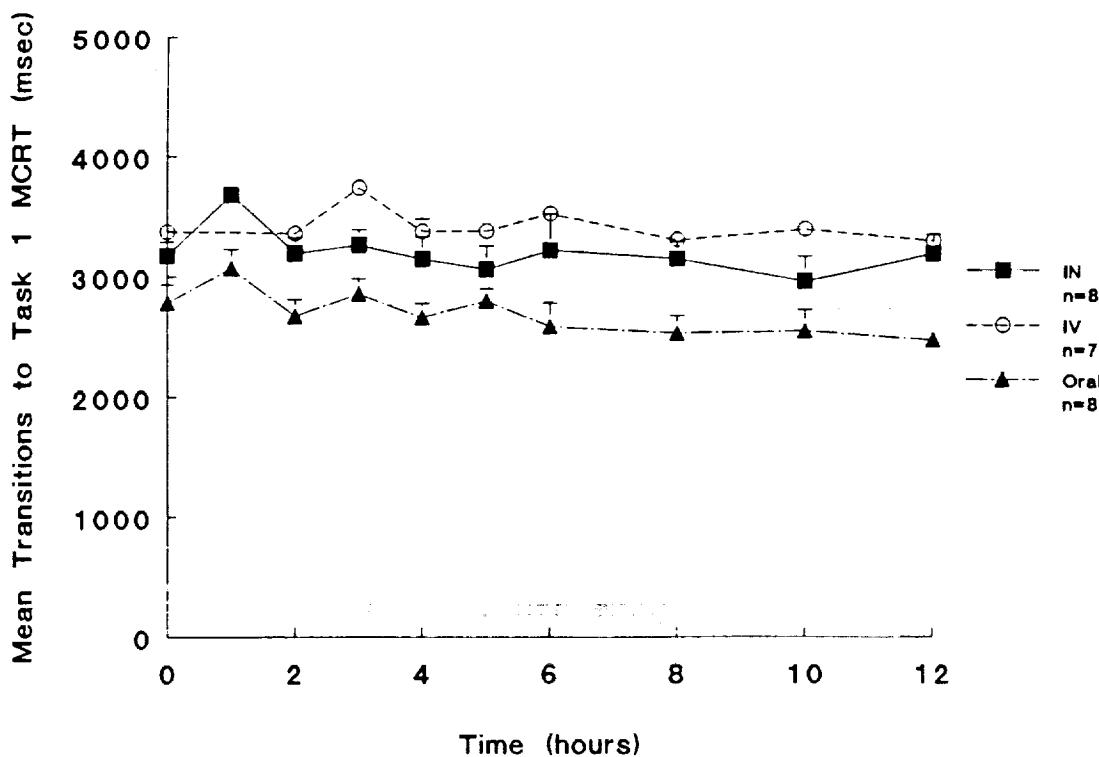


FIGURE 2.- SALIVARY FLOW RATE AND pH AFTER SCOPOLAMINE ADMINISTRATION.

Mean Transitions to Task 1 MCRT



Mean Transitions to Task 2 MCRT

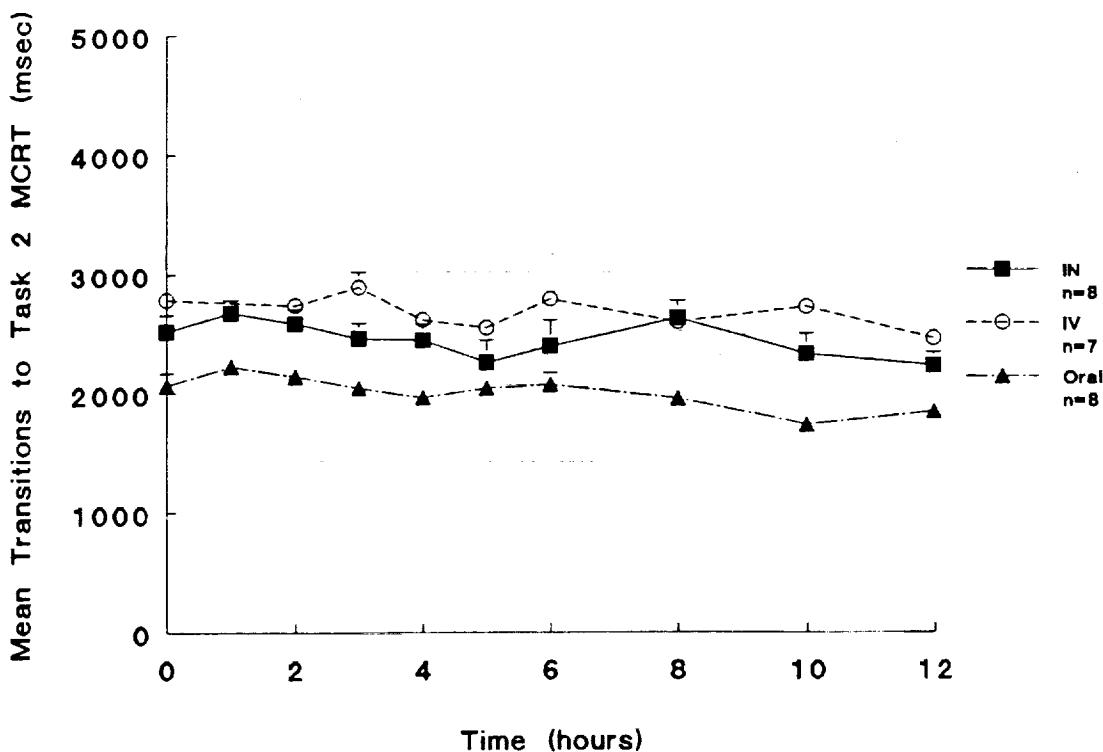


FIGURE 3.- MEAN CORRECT RESPONSE TIMES FOR TRANSITIONS TO TASK ONE AND TASK TWO AFTER SCOPOLAMINE ADMINISTRATION.

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